Use of Calcium Channel Blockers in Cardiovascular Risk Reduction

Issues in Latin America

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Abstract

Cardiovascular disease (CVD) is a continuum that begins with the presence of several risk factors for CVD, including smoking, hypertension, obesity, diabetes mellitus, and high levels of cholesterol, and if unaddressed can result in premature death, ischemic heart disease, stroke, congestive heart failure, and end-stage renal disease. Hypertension is associated with a significant increase in cardiovascular (CV) morbidity and mortality, raising the risk of stroke, myocardial infarction, heart failure, kidney disease, and peripheral arterial disease. In Latin America, the prevalence of hypertension and other CV risk factors has become similar to that seen in more developed countries, increasing the proportion of the population at high risk for CVD and congestive heart failure; however, it is hypertension that is a key driving force behind CV risk in Latin America. Despite the existence of a wide range of antihypertensive agents, BP control and reductions in CV risk remain poor in Latin America and in Hispanics living in the US. Ethnic differences in treatment rates and disease awareness have been well documented. Studies have shown that calcium channel blockers (CCBs; calcium channel antagonists) are at least as effective in reducing BP and improving the CV risk profile as other classes of antihypertensive agents when administered as monotherapy. CCBs have also been shown to be effective when administered as part of combination therapy in both low- and high-risk hypertensive patients, suggesting that CCBs can easily be combined with other antihypertensive classes in order to achieve BP control and CV risk reduction. In patients with hypertension, coronary artery disease, and high cholesterol, CCBs have been associated with beneficial effects on a range of other aspects of the CV continuum, including the vasculature, coronary calcification, and progression of atherosclerosis. CCBs have also been shown to preserve renal function. Unlike diuretics and β-adrenoreceptor antagonists, CCBs are
metabolically neutral, inducing minimal changes in serum lipids and decreasing the incidence of new-onset diabetes compared with other antihypertensive agents. CCBs are well tolerated when administered as monotherapy or combination therapy, with long-acting formulations minimizing adverse events even further compared with short-acting formulations. These characteristics make CCBs an attractive option for the treatment of hypertension and CV risk in Latin America, which remain significant health issues in this region.

1. Update on Cardiovascular (CV) Risk in Latin America and the Importance of Hypertension

The pathophysiology of cardiovascular disease (CVD) has been described as a cardiovascular (CV) continuum that begins with the presence of risk factors for CVD, ultimately resulting in premature death, ischemic heart disease, stroke, and the development of congestive heart failure and end-stage renal disease.[1] The concept of a continuum has expanded into what is now recognized as a cardio-renal continuum, in which kidney damage increases CV risk, and vice versa, in a vicious circle. We now know that the development of CV and renal damage originates in a shared set of risk factors.

The management of patients at risk for CVD includes lifestyle changes with or without pharmacotherapy, and risk stratification at an early stage is highly important for guiding therapeutic decisions.[2] Data suggest that psychosocial stress is among the most important risk factors for CVD in Latin America, along with a history of hypertension;[3] additional risk factors include a history of diabetes mellitus, current smoking, increased waist : hip ratio, hypercholesterolemia, and high alcohol intake.[3-6]

Hypertension, defined as an SBP of ≥140 mmHg and a DBP of ≥90 mmHg,[2,7] is associated with a significant increase in CV morbidity and mortality. Hypertension increases the risk of stroke, myocardial infarction (MI), heart failure, kidney disease, and peripheral arterial disease.[2,8,9] For patients aged 40–70 years, the risk of hypertension-related adverse events doubles with every increase of 20 mmHg in SBP or 10 mmHg in DBP within the BP range of 115/75 to 185/115 mmHg.[10] Thus, the importance of BP control (defined as a BP <140/90 mmHg for hypertensive patients and <130/80 mmHg for diabetic hypertensive patients)[2,11] in reducing the incidence of adverse CV events cannot be underestimated.

A small proportion of patients with stage I hypertension (defined as an SBP or DBP of 140–159 and 90–99 mmHg, respectively[2]) may achieve good BP control with antihypertensive monotherapy, but most patients require two or more agents to achieve BP goals.[2] Despite the fact that a wide range of antihypertensive agents exists, control of BP and reductions in CV risk remain unacceptably poor. In the US during 2005 and 2006, only 64% of hypertensive patients achieved BP control, despite the use of antihypertensive medication.[12] While there were no ethnic disparities reported with respect to BP control rates, differences were seen in other areas; for example, Mexican Americans were less likely to be aware of their hypertension than non-Hispanic Blacks and were less likely to be receiving antihypertensive medication compared with non-Hispanic Whites and non-Hispanic Blacks.[12]

Calcium channel blockers (CCBs; calcium channel antagonists) are attractive therapeutic options in the treatment of hypertension, with increasing evidence that supports their use not only in patients with hypertension but also in normotensive patients with coronary artery disease (CAD). In this paper, we review the existing evidence for CCBs in the management of CV risk reduction, with a particular focus on the scope of the challenges in Latin America.

2. The Reality of CV Risk in Latin America

CVD is one of the leading causes of mortality in Latin America,[13] being responsible for around 800,000 deaths per year (around 25% of all deaths).[14] The death rate from ischemic heart disease and stroke in this region is also increasing; it is expected to triple between 1990 and 2020.[13] Latin America has been said to be in the initial phase of a CAD epidemic (reviewed by Cubillos-Garzon et al.[15]). The average age of the Latin American population is increasing, and with that comes increases in the prevalence of hypertension, obesity, diabetes, and metabolic syndrome – key risk factors in the development of CVD.[15-18] The prevalence of these risk factors in Latin America has become similar to that seen in more developed countries. For example, the prevalence of hypertension in Latin America in the late 1980s and 1990s averaged 20–23%, while the prevalence in the US during a similar period was 24%.[19,20] Similarities in prevalence between Latin America and the US are also seen with obesity and diabetes (reviewed by Cubillos-Garzon et al.[15]).
Estimated total deaths in 23 selected developing countries are expected to rise in 2015 and almost half of these deaths will occur in people younger than 70 years compared with only 27% in high-income countries.\[21\] This figure will rise to 53% in 2030 with an overall share of burden of disease in disability-adjusted life-years of almost 60%. Additionally, the long-term economic savings, by comparing gross domestic product levels under a scenario of achieving a 2% yearly additional reduction in mortality rates from chronic diseases, as recommended by the WHO, would save almost 10% of the expected loss in income in these countries.\[22\]

Hypertension is a key driving force for CV risk in Latin America. However, the incidence of hypertension and other CV risk factors varies widely across the region, probably due to a number of factors, such as differences in the incidences of smoking and obesity, and ethnic variation. Moreover, epidemiological studies in Latin America have been impeded by methodological inconsistencies, such as risk-factor definitions, variations in the age of individuals enrolled, poor sampling techniques, and methods of assessment.\[23\] A recent population-based study of individuals aged 25–64 years in seven Latin American cities reported a prevalence of hypertension that ranged from 24–29% in Santiago (Chile), Barquisimeto (Venezuela), and Buenos Aires (Argentina), to as low as 9% in Quito (Ecuador).\[24\] Another study reported a prevalence of hypertension of 30% among 15- to 85-year-olds in Cordoba (Argentina).\[25\] Diagnosis and management of hypertension in Latin America generally follows the guidelines of the Joint National Committee,\[2\] the WHO/International Society of Hypertension (ISH),\[11\] and the ISH/European Society of Cardiology (ESC).\[26\]

Approximately 80% of the burden of BP-attributable diseases occurs in low- and middle-income countries (Latin America included), with BP-attributable death rates 1.5- to 2-fold higher in low- or middle-income regions compared with high-income regions. A greater proportion of this disease burden occurs in younger people. About half of this burden is in people with an SBP <145 mmHg.\[21\] Many countries, such as Argentina, Brazil, Colombia, Ecuador, Mexico, Peru, and Venezuela, have developed their own guidelines. A Latin American consensus in hypertension and a Latin American consensus in diabetes and hypertension have been published.\[27-29\]

Ongoing issues in antihypertensive therapy in Latin America are the same as those observed elsewhere. For example, BP control rates are unacceptably low, with rates as low as 13% and 15% reported in Argentina and Cuba.\[25,30\] Inadequate financial investment in healthcare represents an additional barrier to successful management of hypertension in Latin America. For example, while 11.6% of the worldwide burden of death and disability from all causes is attributed to developed countries, these countries account for over 90% of healthcare expenditure.\[31\] Hypertension must compete with other chronic diseases that have less of an overall impact on morbidity and mortality for a share of healthcare expenditure, and this may result in a disproportionate distribution of funds with respect to health outcomes. Indeed, data from Mexico indicate that only 6–8% of the total health budget is allocated to hypertension.\[32\] These dismal observations warrant a call to action for improved control of high BP and other CV risk factors across Latin America. Achieving these ambitious goals will require collaborative efforts by many groups, including policy-makers, international organizations, healthcare providers, schools, and society as a whole.\[33\]

### 3. Calcium Channel Blocker (CCB) Monotherapy: BP Control and Associated CV Risk Reduction

When administered as monotherapy, CCBs have generally been shown to be at least as effective, if not more effective, compared with other hypertensive classes in terms of BP control in patients with hypertension. In a crossover study of previously untreated hypertensive patients, CCBs were as effective at reducing SBP as diuretics and significantly (p < 0.005) more effective than ACE inhibitors and β-adrenoceptor antagonists (β-blockers).\[34\] In high-risk patients with hypertension, amlodipine therapy resulted in significantly greater BP reductions than valsartan therapy (17.3/9.9 mmHg vs 15.2/8.2 mmHg; p < 0.0001) and a greater number of patients achieving BP control (62% vs 56%) in the VALUE study,\[35\] (see table I for trial names). Nifedipine monotherapy has also demonstrated good efficacy in hypertensive patients who have at least one additional risk factor; in INSIGHT, a long-acting gastrointestinal transport system (GITS) formulation of nifedipine was as effective as co-amilozide (hydrochlorothiazide [HCTZ] plus amiloride) with respect to reduction in SBP, DBP, and the proportion of patients achieving BP goal (≥50% in both treatment groups).\[36\]

BP reductions were generally similar to those seen with other agents in patients receiving diltiazem in the NORDIL study,\[37\] or verapamil in the CONVINCE trial.\[38\] Effective lowering of SBP and DBP was seen in both groups in the NORDIL study; BP reductions were 20.3/18.7 mmHg in the diltiazem group and 23.3/18.7 mmHg in the diuretic and β-blocker group.\[37\] In the CONVINCE trial, 65.5% of verapamil recipients and 65.9% of patients receiving atenolol or HCTZ achieved a BP target of...
The efficacy of CCBs in lowering BP has also been demonstrated in a number of other large studies in which patients with hypertension were treated with nifedipine,
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CV risk has been associated more strongly with SBP than with DBP. Indeed, it is estimated that around half of all disease burden occurs in individuals with an SBP of 130–150 mmHg. The finding that nifedipine effectively reduces SBP is, therefore, highly important. Of note, in addition to its effectiveness in patients with essential hypertension, nifedipine was shown to be effective at reducing SBP in patients with isolated systolic hypertension in a subanalysis of patients from the INSIGHT trial. Use of CCBs is therefore associated with a reduction in CV risk in a wide range of hypertensive patients.

CCBs are associated with substantial improvements in the CV risk profile. Compared with placebo, CCBs have been shown to significantly reduce the incidence of CV events in patients with hypertension. When CCBs are compared with other antihypertensive classes, the effect on CV outcomes is generally similar. The reduction in the incidence of stroke and MI was similar between amlopidine monotherapy and both valsartan and chlorothalidone monotherapy in two studies. In the ALLHAT trial, 11.3% and 11.5% of patients with hypertension and at least one CV risk factor receiving amlopidine and chlorothalidone, respectively, experienced the primary combined endpoint of fatal CAD or nonfatal MI. The VALUE study had a combined primary endpoint of cardiac mortality and morbidity, which occurred in 10.4% and 10.6% of patients receiving amlopidine and valsartan, respectively.

In the INSIGHT study, nifedipine GITS monotherapy was as effective as co-amilozide for reducing the incidence of the primary composite endpoint of CV death, MI, heart failure, or nonfatal stroke; 6.3% and 5.8% of nifedipine and co-amilozide recipients, respectively, experienced these outcomes, and these rates corresponded to 18.2 and 16.5 primary endpoints per 1000 patient-years (p=0.34). Since the baseline data for the Framingham risk equation predicts an event rate of 34.5 primary endpoints per 1000 patient-years, treatment with nifedipine and co-amilozide reduced the number of CV events by approximately half of the expected rate. A subanalysis of hypertensive diabetic patients enrolled in the INSIGHT study showed that while there was no difference in the primary endpoint between treatment groups, significantly fewer hypertensive diabetic patients receiving nifedipine than those receiving co-amilozide experienced the secondary composite endpoint of all-cause mortality, death from a vascular cause, and death from a nonvascular cause (14.2% vs 18.7%; p=0.03). Similarly, patients taking verapamil or atenolol or

### Table I. Trial names

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Name</th>
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<tr>
<td>ACCOMPLISH</td>
<td>Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension</td>
</tr>
<tr>
<td>ACTION</td>
<td>A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system</td>
</tr>
<tr>
<td>ADVANCE-Combi</td>
<td>Adalat CR and Valsartan Cost-Effectiveness Combination</td>
</tr>
<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial</td>
</tr>
<tr>
<td>ASCOT-BPLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm</td>
</tr>
<tr>
<td>BENEDICT</td>
<td>Bergamo Nephrologic Diabetes Complications Trial</td>
</tr>
<tr>
<td>CAMELOT</td>
<td>Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis</td>
</tr>
<tr>
<td>COACH</td>
<td>Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>Controlled Onset of Verapamil Investigation of Cardiovascular Endpoints</td>
</tr>
<tr>
<td>ENCORE</td>
<td>Evaluation of Nifedipine and Cervastatin On Recovery of coronary Endothelial function</td>
</tr>
<tr>
<td>FACET</td>
<td>Fosinopril vs Amlodipine Cardiovascular Events Randomized Trial</td>
</tr>
<tr>
<td>INSIGHT</td>
<td>International Nifedipine GastroIntestinal Transport System Study: Intervention as a Goal in Hypertension Treatment</td>
</tr>
<tr>
<td>INVEST</td>
<td>International Verapamil-Trandolapril Study</td>
</tr>
<tr>
<td>J-MIND</td>
<td>Japan Multicenter Investigation of Antihypertensive Treatment for Nephropathy in Diabetes</td>
</tr>
<tr>
<td>M-FACT</td>
<td>Metoprolol Succinate-Felodipine Antihypertension Combination Trial</td>
</tr>
<tr>
<td>MARVAL</td>
<td>Microalbuminuria Reduction With Valsartan;</td>
</tr>
<tr>
<td>MIDAS</td>
<td>Multicenter Iradipine Diuretic Atherosclerosis Study</td>
</tr>
<tr>
<td>NICE-Combi</td>
<td>Nifedipine and Candesartan Combination</td>
</tr>
<tr>
<td>NORDIL</td>
<td>Nordic Diltiazem</td>
</tr>
<tr>
<td>REACH</td>
<td>Reduction of Atherothrombosis for Continued Health</td>
</tr>
<tr>
<td>TALENT</td>
<td>STudy EvAluating the Efficacy of Nifedipine GITS – Telmisartan Combination in Blood Pressure Control</td>
</tr>
<tr>
<td>VALUE</td>
<td>Valsartan Antihypertensive Long-term Use Evaluation</td>
</tr>
<tr>
<td>VHAS</td>
<td>Verapamil in Hypertension and Atherosclerosis Study</td>
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<140/90 mmHg. The efficacy of CCBs in lowering BP has also been demonstrated in a number of other large studies in which patients with hypertension were treated with nicardipine, felodipine, or nitrendipine.

CV risk has been associated more strongly with SBP than with DBP. Indeed, it is estimated that around half of all disease burden occurs in individuals with an SBP of

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HCTZ experienced a similar rate of stroke, MI, or CVD-related death in the CONVINCE study (hazard ratio [HR] 1.02; 95% CI 0.88, 1.18).

### 4. CCBs in Combination Therapy: BP Control

As mentioned above, evidence from previous studies suggests that many patients require combination therapy in order to achieve BP goals, particularly those at high CV risk. The optimal combination of antihypertensive agents, however, remains to be established. CCBs have been shown to effectively reduce BP when administered as part of combination therapy for hypertension in both low- and high-risk patients. In the ASCOT-BPLA study, the combination of amlodipine and the ACE inhibitor perindopril was associated with a similar reduction in both SBP and DBP as the combination of atenolol and a thiazide in high-risk patients (27.5/17.7 mmHg vs 25.7/15.6 mmHg). In the ACCOMPLISH study, high-risk patients received amlodipine plus benazepril or benazepril plus HCTZ. Compared with benazepril plus HCTZ, BP control rates were higher and SBP reductions were greater with amlodipine plus benazepril.

Adding an angiotensin II type 1 receptor antagonist (angiotensin receptor blocker [ARB]) to nifedipine was shown to yield additional BP control to that provided by either agent alone in patients with mild-to-moderate hypertension. Importantly, the reduction in SBP was greater with the combination of nifedipine and losartan than with either agent alone. After 8 weeks of therapy, BP reduction was 23.3/15.3 mmHg in the combination group, and 16.3/11.4 mmHg and 18.9/12.5 mmHg in the losartan and nifedipine groups, respectively (losartan plus nifedipine vs losartan; p < 0.05).

Adding an ARB to amlodipine has also been shown to enable greater BP reductions and increased BP control compared with either agent alone. In the COACH study a combination of amlodipine and olmesartan medoxomil produced a BP reduction of 30.1/19.0 mmHg compared with 19.7/12.7 mmHg and 16.1/10.2 mmHg with amlodipine and olmesartan monotherapy, respectively. In a separate study, a combination of amlodipine and valsartan produced BP reductions from baseline of 28.4/18.6 mmHg compared with 24.1/15.6 mmHg and 19.8/13.3 mmHg with amlodipine and valsartan monotherapy, respectively.

In the NICE-Combi study, Japanese patients with essential hypertension whose BP remained uncontrolled after an 8-week course of candesartan monotherapy received either nifedipine controlled release plus candesartan combination therapy, or an increased dose of candesartan. As expected, more patients achieved BP goal with combination therapy than with uptitrated candesartan, and reductions in both SBP and DBP were significantly greater (p < 0.0001) [figure 1]. When CCBs were compared in another group of Japanese patients with essential hypertension in the ADVANCE-Combi study, nifedipine controlled release plus valsartan demonstrated significantly superior reductions in both DBP and SBP than amlodipine plus valsartan after 16 weeks (34.0/20.1 mmHg vs 27.0/15.9 mmHg; p < 0.05). The proportion of patients achieving BP goal was also significantly higher with nifedipine plus valsartan compared with amlodipine plus valsartan (61.2% vs 34.6%; p < 0.001).

CCBs are effective and well tolerated when combined with β-blockers for the treatment of hypertension. In M-FACT, patients with uncomplicated hypertension were randomized to receive one of 16 treatment regimens comprising extended-release felodipine or metoprolol succinate monotherapy or a combination of the two agents. BP reductions were similar with low-dose combination therapy and monotherapy, and combination treatment was better tolerated.

Verapamil-based treatment was as effective as amlodipine-based therapy at lowering BP in patients with hypertension and CAD in INVEST. In this trial, patients were randomized to receive either sustained-release verapamil or amlodipine, andtrandolapril and/or HCTZ was added to achieve BP goals. Joint National Committee on Prevention, Detection, Evaluation,
and Treatment of High Blood Pressure (JNC VI) goals for SBP and DBP were achieved in 65.0% and 88.5% of CCB recipients and 64.0% and 88.1% of patients receiving atenolol-based therapy.

There is also evidence that CCBs effectively reduce BP compared with placebo in patients receiving medication to treat CAD. The CAMELOT study evaluated patients with CAD and normal BP (<140/90 mmHg) who received placebo, amlodipine, or enalapril in addition to their existing medications, the most frequent (taken by >70% of patients) being β-blockers, statins, and aspirin (acetylsalicylic acid). After 24 months of treatment, recipients of amlodipine and enalapril had reductions in BP (4.8/2.5 mmHg and 4.9/2.4 mmHg, respectively; p < 0.001 vs placebo), while placebo recipients had an increase in BP by 52/37 mmHg (0.7/0.6 mmHg). In the ACTION study, patients with stable angina received either nifedipine GITS or placebo on top of best practice CV therapy (β-blockers and/or organic nitrate, administered either as needed or as daily maintenance therapy). Control of both SBP and DBP was significantly greater with nifedipine than with placebo in this study. At baseline, 52% of patients had a BP ≥140/90 mmHg; at study end, 65% of patients who received nifedipine plus best practice CV therapy were controlled, compared with 53% of patients who received placebo plus best practice CV therapy.

The ongoing TALENT study is investigating the efficacy of combining nifedipine GITS with telmisartan, an ARB with a long half-life, in approximately 400 patients at high CV risk because of the presence of diabetes, subclinical damage, or a metabolic syndrome.

5. CCBs in Combination Therapy: CV Risk Reduction

The combination of amlodipine and perindopril was associated with a nonsignificant 10% decrease in the incidence of nonfatal MI and fatal CAD compared with the combination of atenolol plus a thiazide in the ASCOT-BPLA study. However, compared with patients receiving atenolol/thiazide therapy, amlodipine/perindopril recipients experienced a decreased incidence of all-cause mortality (11% reduction; p = 0.025) and fatal and nonfatal stroke (23% reduction; p = 0.0003). In the ACCOMPLISH study, the time to first CV morbidity or mortality was longer with amlodipine plus benazepril than with benazepril plus HCTZ, signifying better CV protection.

A similar reduction in CV events occurred in patients with CAD receiving CCBs in addition to existing therapies. Among patients with CAD and normal BP in the CAMELOT study, the reduction in CV events was similar between amlodipine and enalapril (HR 0.81; 95% CI 0.63, 1.04; p = 0.10), and was significantly greater with amlodipine than with placebo (HR 0.69; 95% CI 0.54, 0.88; p = 0.003). There was no difference in CV events between the enalapril and placebo groups (HR 0.85; 95% CI 0.67, 1.07; p = 0.16). In the ACTION study, nifedipine GITS plus best practice CV therapy was associated with significantly longer CV event- and procedure-free survival than with placebo plus best practice CV therapy (figure 2). In addition, a subanalysis of the ACTION trial revealed that nifedipine GITS was associated with a significant reduction in the incidence of heart failure and the need for coronary angiography and bypass surgery. Among those with elevated BP at baseline, a 13% reduction in death and major CV events was observed.

In INVEST, a similar incidence of the primary endpoint (all-cause death, nonfatal MI, or nonfatal stroke) was seen in patients with hypertension and CAD treated with a CCB or non-CCB strategy. The study, which enrolled almost 14,000 patients, showed no significant difference between the two treatment arms for the primary endpoint (RR 0.98; 95% CI 0.90, 1.06).

These data suggest that CCBs can easily be combined with other antihypertensive classes, including ACE inhibitors and ARBs, in order to achieve BP control and CV risk reduction beyond that achieved with the respective monotherapies. Of note, there is a paucity of specific data available on CCBs, alone or in combination, for the treatment of hypertension or other CV disorders specifically in Latin America. However, recent registry data suggests that guideline-recommended treatment of hypertension in Latin America is improving. Baseline data from the REACH registry indicated that nearly 95% of Latin American patients either at risk of or with established CVD were treated with at least one antihypertensive agent. Similar to North America, β-blockers, ACE inhibitors, diuretics, and CCBs were most often prescribed.

Despite the broad application of antihypertensive agents, the REACH registry data demonstrates that work is needed to bring patients to their BP goal, as >50% of Latin American patients were not at target BP levels. Combination approaches were not described in these analyses, and direct morbidity and mortality outcomes due to poor BP control cannot be inferred; however, it is clear that optimal antihypertensive regimens require further evaluation in Latin American practice.

6. Additional Benefits of CCBs

As well as effects on BP control and CV risk reduction, CCBs have been associated with effects on a range of other aspects of the CV continuum. In patients with essential hyperten-
sion, nifedipine monotherapy has been shown to improve endothelial function, oxidative stress, and antioxidative capacity. These beneficial antioxidant effects of CCBs have also been seen with amlodipine and verapamil. Nifedipine has been shown to improve endothelial function in patients with familial hypercholesterolemia. In the ENCORE study in patients with CAD, coronary endothelial function was improved to a greater extent with nifedipine than with either cerivastatin or placebo. In the ENCORE II study, significant improvements in coronary endothelial function that persisted for at least 2 years, and a positive, non-significant trend in reduction of atheroma volume were observed with nifedipine.

A non-significant trend towards a lower rate of mean intimal thickening with CCBs compared with diuretics was seen in two 3- or 4-year studies. In VHAS, verapamil 240 mg once daily was compared with chlorthalidone 25 mg once daily. Changes in intima-media thickness and between-group differences were small, but when analyzed by intima-media thickness strata, patients with plaques receiving verapamil had a significantly lower rate of CV events than chlorthalidone recipients. In MIDAS, patients randomized to receive isradipine showed a trend towards a greater incidence of CV events compared with HCTZ recipients, but the between-group difference was not significant.

CCBs have also demonstrated a positive effect on vasculature in patients with hypertension, CAD, or raised serum cholesterol levels. Ancillary studies associated with the INSIGHT trial investigated the effects of nifedipine versus co-amilozide on carotid vascular wall changes and progression of coronary calcification in high-risk hypertensive patients. Nifedipine was shown to have an effect on coronary calcium deposition over a 3-year period, compared with co-amilozide, with a total calcium score of 39.9% versus a score of 77.8% in the co-amilozide group (p = 0.02). In patients who completed the study investigating carotid wall changes, both groups had similar reductions in BP; however, intima-media thickness progression was seen in patients receiving co-amilozide (0.0077 mm/year) but not in the nifedipine group (-0.0007 mm/year; p = 0.003 vs co-amilozide) [figure 3]. Similarly, there were significant differences between the nifedipine and co-amilozide groups with respect to the changes in intima-media thickness (-0.004 vs +0.034 mm; p = 0.002) and cross-sectional area intima-media thickness (-0.332 vs +0.518 mm²; p = 0.005). Amlodipine also significantly reduced carotid intima-media thickness compared with placebo (-0.013 vs +0.033 mm; p = 0.007) in patients with CAD. In another study of patients with CAD, nifedipine had no effect on existing atherosclerotic lesions, but significantly reduced the rate of formation of new lesions per patient by 28% compared with placebo (0.59 vs 0.82; p = 0.034).

A meta-analysis of clinical trials that included data from 100 studies of eight dihydropyridine and four non-dihydropyridine CCBs showed no increase in serum lipid levels in patients receiving these agents. The progression of atherosclerosis in symptomatic patients with elevated serum cholesterol levels...
was reduced in patients receiving CCBs plus pravastatin versus pravastatin alone, and in a cohort of Japanese patients with CAD receiving nifedipine versus ACE inhibitors.[72,76] In the Japanese study, nifedipine also reduced the number of new lesions compared with ACE-inhibitor treatment, although the difference was not significant (p=0.072).[76] In the ACTION study, nifedipine was associated with a positive effect on coronary angiography, with the need for the procedure being reduced by 21% and 16% in normotensive and hypertensive patients, respectively; this was thought to be attributable to the anti-anginal, rather than BP-lowering, effects of this class of agents.[61]

CCBs have also been associated with beneficial effects on other systems. Analysis of the INSIGHT study results according to renal function showed that nifedipine may preserve renal function to a greater degree than diuretic-based treatments, with renal insufficiency occurring in significantly fewer patients receiving nifedipine than co-amilozide (2% vs 5%; p<0.01).[78] In addition, both amlodipine and nifedipine have also been associated with a lower rate of new-onset diabetes than diuretics and β-blockers.[36,48] In the INSIGHT study, 4.3% of patients receiving nifedipine developed diabetes compared with 5.6% of patients in the co-amilozide group (p=0.02).[36] While there was a 30% reduction in new-onset diabetes in patients receiving amlodipine compared with atenolol plus a thiazide in the ASCOT-BPLA study (HR 0.70; 95% CI 0.63, 0.78; p<0.0001).[48] The lower incidence of new-onset diabetes seen in patients receiving CCBs in these studies may, in part, be a reflection of the increased incidence of new-onset diabetes experienced by individuals with hypertension treated with β-blockers and/or thiazide diuretics rather than protection invoked by CCBs per se.[79]

Long-term treatment with CCBs was effective at halting the progression of nephropathy in diabetic patients with hypertension and normoalbuminuria or microalbuminuria in a number of trials of between 36 weeks’ and 3.6 years’ duration (table II).[80,82-86] No significant increases from baseline in mean urinary albumin excretion were seen in any of the studies, and between 0% and 28% of individuals progressed from normo- to micro- or macroalbuminuria in these studies.[80,82-86] In one study, no significant difference in the incidence of persistent microalbuminuria was seen between patients receiving verapamil 240 mg/day or placebo.[80] No patients in any study receiving CCBs, or comparator agents, experienced a doubling of serum creatinine or onset of end-stage renal failure throughout active therapy.[82,84-86] A single study comparing CCBs with an ARB demonstrated a significant benefit for valsartan over amlodipine in diabetic patients with microalbuminuria over 24 weeks with similar reductions in BP.[81] CCBs compared with ACE inhibitors showed no between-treatment differences favoring a specific therapy.[80,82-86] A meta-analysis using data from four of these studies showed a significantly greater reduction in the risk of developing kidney disease (micro- or macroalbuminuria) with ACE inhibitors compared with CCBs (RR 0.58; 95% CI 0.40, 0.84).[87] However, no significant between-group difference in all-cause mortality was seen when data from six trials were analyzed (RR 0.84; 95% CI 0.26, 2.73).[87]

### 7. Tolerability of CCBs

CCBs have been shown to be well tolerated both as monotherapy and when combined with ACE inhibitors or ARBs. Adverse effects most commonly associated with CCBs include dizziness, headache, flushing, and peripheral edema.[35,36,48-50,53,57,58] Generally, adverse events are less prevalent with the long-acting CCB formulations; for example, the incidences of flushing, headache, dizziness, peripheral edema, and heart palpitations/tachycardia have been reported as being <5% in several studies of controlled-release nifedipine.[50,53,54,58] In addition, combination therapy with a CCB plus an ACE inhibitor has been shown to reduce the incidence of edema associated with CCB use.[88]

Several antihypertensive agents have been shown to induce adverse metabolic effects; for example, β-blockers increase triglycerides and decrease high-density lipoprotein (HDL)-cholesterol, and diuretics lower serum potassium levels and increase serum urea and uric acid levels.[34] In contrast, CCBs are generally metabolically neutral, with studies reporting no

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**Fig. 3.** Intima-media thickness progression rate with nifedipine and co-amilozide in the INSIGHT study. * p<0.01, ** p<0.001 vs zero within treatment group.[71]
effect of CCBs on serum levels of triglycerides, total cholesterol, low-density lipoprotein-cholesterol, or HDL-cholesterol.\[72,76\] Furthermore, as mentioned above, the risk of new diabetes is substantially lower than that observed with other anti-hypertensive classes.\[36,48,89\]

### 8. The Future of CCBs in the Treatment of Hypertension

CCBs are likely to remain a mainstay of treatment for hypertension in Latin America. Even as monotherapy, CCBs have demonstrated effective BP control (and, importantly, SBP control), with 70% of patients in the INSIGHT study achieving BP goal when receiving nifedipine.\[36\]

CCBs have also been shown to improve the CV risk profile to a greater degree than that expected by their BP-lowering effects alone and to provide additional advantages in terms of renal and vascular protection, reduction in new-onset diabetes cases, and lack of effect on metabolic parameters. Given that the majority of patients on antihypertensives will eventually require multiple medications to control their BP, the place of CCBs in hypertension management will most likely be as part of combination therapy. Indeed, CCBs have been shown to be amenable to combination with other antihypertensive drugs, including ARBs and ACE inhibitors. The additive effect observed with combination therapy most likely occurs because of differing modes of action providing synergistic or complementary effects.

### 9. Conclusions

A main goal of antihypertensive treatment is to increase the length and quality of life in patients with this condition.\[90\] Several studies and meta-analyses have demonstrated that CCBs effectively reduce BP and CV morbidity and mortality, and display additional beneficial effects on vasculature and renal function. CCBs are also well tolerated and are amenable

#### Table II. Effect of calcium channel blockers (calcium channel antagonists) on proteinuria in adult patients with hypertension and type 2 diabetes mellitus\[^a\]

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design (duration)</th>
<th>Drug and dosage (mg/day)</th>
<th>No. of patients</th>
<th>Mean urinary albumin excretion (mg/day)</th>
<th>No. of patients reverting from normo- to micro-or macroalbuminuria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>baseline</td>
<td>endpoint</td>
</tr>
<tr>
<td>BENEDICT study[^80^]</td>
<td>r, db, mc, pc (median 3.6 y)</td>
<td>Trandolapril 2</td>
<td>301</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Verapamil 240</td>
<td>303</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trandolapril/verapamil 2/180</td>
<td>300</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>300</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MARVAL study[^81^]</td>
<td>r, db, mc (24 wk)</td>
<td>Valsartan 80</td>
<td>169</td>
<td>microalbuminuric</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine 5</td>
<td>163</td>
<td>microalbuminuric</td>
<td>80</td>
</tr>
<tr>
<td>J-MIND study[^82^]</td>
<td>r, ol (24 mo)</td>
<td>Nifedipine 20–60</td>
<td>228</td>
<td>45</td>
<td>64</td>
</tr>
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<td></td>
<td></td>
<td>Enalapril 5–20</td>
<td>208</td>
<td>42</td>
<td>74</td>
</tr>
<tr>
<td>Chan et al.[^83^]</td>
<td>r, db, pc (52 wk)</td>
<td>Enalapril 10</td>
<td>50</td>
<td>88</td>
<td>77*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nifedipine 40</td>
<td>52</td>
<td>82</td>
<td>97</td>
</tr>
<tr>
<td>FACET study[^84^]</td>
<td>r, ol (3.5 y)</td>
<td>Fosinopril 20</td>
<td>189</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine 10</td>
<td>191</td>
<td>35*</td>
<td>19</td>
</tr>
<tr>
<td>Scognamiglio et al.[^85^]</td>
<td>r, db (36 wk)</td>
<td>Captopril 50–100</td>
<td>38</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrendipine 20–40</td>
<td>37</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Velussi et al.[^86^]</td>
<td>r, db (3 y)</td>
<td>Cilazapril 2.5</td>
<td>13</td>
<td>normoalbuminuric</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine 5</td>
<td>13</td>
<td>normoalbuminuric</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cilazapril 2.5</td>
<td>9</td>
<td>microalbuminuric</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amlodipine 5</td>
<td>9</td>
<td>microalbuminuric</td>
<td>56</td>
</tr>
</tbody>
</table>

\[^a^\] Supplementary data obtained from Strippoli et al.[^87^] (2005).

\[^db^\] = double-blind; \[^mo^\] = months; \[^mc^\] = multicenter; \[^n/a^\] = not applicable; \[^NR^\] = not reported; \[^ol^\] = open-label; \[^pc^\] = placebo-controlled; \[^r^\] = randomized. * \(p < 0.01\) vs placebo; † \(p < 0.01\) vs baseline; ‡ \(p < 0.05\) vs fosinopril.
to combination therapy with either ARBs or ACE inhibitors. Therefore, these agents represent an appropriate choice of antihypertensive agent in Latin America, where hypertension and CV risk remain substantial health issues.

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Latin American Expert Group on Cardiovascular and Metabolic Risk:
Luis Alcocer, MD, MPH; Mario Bendersky, MD, PhD; Julio Acosta, MD; Miguel Urina-Triana, MD, FACCF; Hugo Hernández, MD; Oscar Sada, MD; Alberto Rubio, MD; Pablo Rodríguez, MD; Alberto Cafferata, MD; Andréia Loures-Vale, MD; Celso Amodeo, MD; Mauricio Varela Ramos, MD; Franklin Haase, MD; Bolivar Tejada, MD; Roberto Lecaro, MD; Carlos Galán, MD; Roberto López, MD; Marco Antonio Lavagnino, MD (Bayer Schering Pharma Staff); and Guido Senatoro, MD (Bayer Schering Pharma Staff).

Dr Alcocer serves as a consultant and has received fees from speaking engagements from Abbott Laboratories, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Merck, Novartis, Pfizer, Roche, sanofi-aventis, and Servier. Dr Urina-Triana has received grants from Bayer, Bristol-Myers Squibb, Frosst Laboratories, Novartis, Pfizer, and sanofi-aventis. Dr Bendersky and Dr Acosta have no conflicts of interest.

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